A Study of Self-Diffusion in Biomolecule Suspensions and Colloidal Suspensions by Brownian-Dynamics Simulations

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論文内容要旨

The self-diffusion of biomolecules in a solution is an important problem to study drug delivery, digestion, and functions of organs in human body. Thus research interest of this problem is increasing in these decades. However understanding of it is not easy because of mainly two reasons. One of the reasons is that it is difficult to know the interaction between biomolecules. The main origin of interaction between biomolecules is surface charge on them. Since the small charge of devices for the measurement affects the state of the solution and molecules, the direct measurement of interaction force between biomolecules is much more difficult than that of colloids. Additionally, the hydrodynamic interaction between particles is also important to consider the motion of biomolecules. However, since the shape and charge condition of biomolecules are not a simple spherical form, to predict the interaction force from microscopic point of view is also difficult problem in both of theory and simulation. The other problem occurs when the volume fraction is high. In the dilute region, the density fluctuation of suspension is linear, and the time development of density field can be well described by linear diffusion equation. But in dense region, the diffusion coefficient of the system decreases as ϕ increases, and the density fluctuation is affected by higher order terms. In order to study the self-diffusion of biomolecules in dense regions, construction of a theoretical framework to study dynamics of colloidal suspension is necessary.

To solve the first problems, the effective models to study the interaction between biomolecules have been proposed. The theory proposed by Derjaguin and Landau, and independently Verwey and Overbeek, which is called DLVO theory, is one of the most famous theories to study the interaction between charged colloidal suspension and biomolecules. In DLVO theory, the charges of particles are assumed to be uniform on their surface and result in spherically screened interactions between the electric double layers around particles. This assumption is valid up to the biomolecules that has of the order 10 charges. For molecules with smaller number of charges, the discreteness of the charge is no more negligible, and thought to be reason of phase behavior. There are also simulation studies to model biomolecules directly and with simplifications. Problem of these approaches is that the models still have degrees of freedom depending of structure of molecules and

state of the solution.

The second problem is strongly connected to the problem of supercooled liquid and glass transition. Glass transition is a phenomenon that the viscosity of fluids dramatically increases with decreasing the temperature or the volume fraction of the system near the glass transition point, and finally looses fluidicity and freezes without clear structural change that is observed in crystallization. As glass transition approaches from liquid state, several time scales that are not observed in liquid state appears and the dynamics of the system becomes complex. This is typically observed in the time development of one kinds of density correlation function called self-intermediate scattering function $F_S(k,t)$. In liquid state, $F_S(k,t)$ shows a single exponential like decay. Near the glass transition point, this becomes two-step non-linear relaxation. This phenomenon is observed in many kinds of systems including oxides, polymer mixtures, metals, and colloidal suspensions. In order to understand these phenomena, mode-coupling theory (MCT) was proposed in early 1980s, and later extended for colloidal suspensions. Recently, possibilities that biomolecules in solution also shows glass transition have reported experimentally. From a viewpoint of universality, the glass transition and dynamics of supercooled liquid of solution of biomolecules can be explained by same theories to other glass forming systems.

Recently, Tokuyama *et al.* has proposed a simple model potential to study self-diffusion of biomolecules by means of theoretical analyses based on his mean field theory. They obtained a simple form of model interaction of form $U(r) = k_B T\left(\sigma/(r-b\sigma)\right)^6$ with $b = 0.25$ and tested of this potential by Brownian-dynamics simulation showed good agreement with experimental results of self-diffusion coefficients of biomolecules. As applications of this study, we can consider following directions. One is modifying this potential to be more realistic. As mentioned before, biomolecules have non-uniform charges on their surface. It is reported the existence of weak attractive force between molecules is important to reproduce the phase diagram of proteins. Thus it is worth to consider an additional attractive force to the modified soft sphere potential. The other is test of the MCT to this model potential for studying dynamics of dense suspension of biomolecules. Since the modified soft sphere model is written in a simple form, it is suitable for Brownian-dynamics simulation and to calculate a physical quantity called structure factor $S(q)$ which is used for the input of MCT. From a viewpoint of universality, MCT for colloidal suspension can be used for the study of self-diffusion of biomolecules. It is worth to investigate how much MCT can reproduce the characteristic feature of the modified soft sphere potential that can explain self-diffusion of biomolecules.

As stated above, the objective of the present thesis of the present study is as follows:

(1) To extend the modified soft sphere model by adding attractive force.

(2) To test MCT for study of biomolecules by using simulation results of modified soft sphere system.

(3) To explore how to overcome problems of MCT.

Chapter 2 is devoted to introduce our simulation model. Our starting equation to study self-diffusion for suspensions of biomolecules is Langevin equation with hydrodynamic interaction. However, to solve hydrodynamic interaction in Brownian dynamic simulation is technically difficult. From a consideration based on a stand point of mean field theory, we neglect long-time hydrodynamic interaction which makes shift for the critical point, and takes into account short-time hydrodynamic interactions by using short-time

self-diffusion coefficient $D_S^S(\phi)$. As an effective model of direct interactions between particles, we use soft sphere interactions. The simulation techniques related to Brownian-dynamics simulations and molecular-dynamics simulations are also summarized in this chapter.

In chapter 3, we present a framework to construct effective interactions that is suitable for the study of self-diffusion of biomolecules. From analyses of experimental data of self-diffusion coefficients of biomolecules, forms of model interactions are restricted by following two conditions:

(1) From a consideration of a first principle theory, $\kappa = 2$ corresponds to repulsive interaction should have an exponent $n = 6$.

(2) $D_S^S(\phi)$ of a suspension with the model interaction also should obey that of hard sphere suspension, since MFT curve which is used for fitting includes an analytical form of short-time self-diffusion coefficient $D_S^S(\phi)$ for hard sphere suspension. From condition (1), we first tested a conventionally used soft sphere potential with exponent $n = 6$ which has a form $U(r) = k_B T\left(\sigma / r\right)^6$.

However simulation result of D_S^L for conventionally used soft sphere potential showed deviation from the MFT prediction especially at high volume fraction region. In order to overcome this problem, we modified the potential into a form $U(r) = k_B T\left(\sigma / (r - b\sigma)\right)^6$ with a new parameter b. Using this modified soft sphere model, we carried out BD and MD simulation with different values of b and compared $D_S^{L(MD)} / D_S^{L(BD)}$ which is expected to correspond to $D_S^S(\phi)$ of the soft sphere system. As a result, we found that $D_S^{L(MD)} / D_S^{L(BD)}$ of a modified soft sphere interaction with $b = 0.25$ shows good agreement with $D_S^S(\phi)$ for hard sphere system. Next, we checked condition (1) by investigating behavior of D_S^L for $b = 0.25$ and found it obeys to MFT curve with $\kappa = 2$. The ϕ dependence of D_S^L for modified soft sphere model with $b = 0.25$ have similar behavior to that of biomolecules if we scale ϕ by its critical value ϕ_c. Thus we successfully constructed a model interaction between biomolecules in a quite simple form. As an application, these frameworks were also applied to a modified 6-4 type Lennard-Jones interaction, which is obtained by an extension of the modified soft sphere interaction. From analyses of $D_S^{L(MD)}$ and $D_S^{L(BD)}$, we found that $b = 0.30$ is a reasonable value and satisfies conditions (1) and (2). Thus our model can be extended for different kinds of attractive interaction without changing dynamical behavior of D_S^L.

In chapter 4, we tested mode-coupling theory (MCT) for the study of self-diffusion of suspensions in high-density region by comparing it to BD simulation results. Using simulation result for the modified soft sphere mixture, which is mainly discussed in chapter 2, we calculated structure factor $S(q)$ and numerically solved MCT equations by using them as inputs. We compared MCT solutions to BD simulation results. At low volume fraction region, D_S^L of MCT solution showed larger values than that of simulation results. This is because MCT is a theory for liquid state and not suitable to describe the behavior at low-density region. At high volume fraction region, D_S^L of MCT obeys to MFT curve with $\kappa = 2$. We further tested MCT by comparing the mean square displacement $M_2(t)$ to simulation results from a stand point of MFT. MFT states that the state of the system can be determined by the value of D_S^{L*} and if the value of D_S^L is same, even for different kinds of systems, time development of $M_2(t)$ obeys one master curve. From comparisons of $M_2(t)$ of MCT to that of simulation results with same values of D_S^L, we found that the MCT solutions has always smaller values than that of simulation results in intermediate time region, and that deviation grows bigger at higher volume fraction. Same tendency was also observed in

comparison of MCT solutions for binary Lennard-Jones mixture and corresponding BD simulations. Thus this deviation is one of essential problem that MCT has and its origin comes from the type of projection operator method that is used in the derivation of MCT.

In chapter 5, a possibility of modified form of MCT equation is proposed. We review the approximation that is used in the derivation of the memory functions of MCT, and show that usually neglected part in the MCT approximation contains a term that has a same order to that of non-neglected part.

From this finding, we propose a modified MCT equation with a new correction parameter $\Delta(q,k)$. By assuming $\Delta(q,k)$ as a positive constant Δ for simplicity, we tested our modified MCT equation by comparing numerical solutions of it to BD simulation results in several systems. First, we determine the value of Δ so that the behavior of D_S^L at low volume fraction coincides with that of simulation results. We found that by choosing value of Δ properly, D_S^L of modified MCT solutions obey a MCT curve obtained for the simulation results. However, from the comparison of $M_2(t)$, the deviation was still found same as in comparison of standard MCT solution to simulation results. We also checked self-intermediate scattering function $F_S(q,t)$ and non-Gaussian parameter $\alpha_2(t)$. To overcome this problem, mode coupling theory based on other types of projection operator method is needed.

Main findings and statements of the present thesis are as follows:

- As an extension of modified sphere model, we considered 6-4 Lennard-Jones (LJ) with a parameter b in the denominator of repulsive part and attractive part. By considering the condition that the short-time self-diffusion of biomolecules obeys that of hard sphere suspension, we determined $b = 0.30$. Thus we have shown that the scheme that is used to derive the modified soft sphere model also works for different types of potentials.
- The mode coupling theory (MCT) was numerically solved by using structure factor $S(q)$ obtained by BD simulations as inputs to the theory and its dynamics was compared to that of BD simulation results. MCT solution showed quantitatively different behavior from that of simulation results, but fitting results by mean field theory (MFT) showed that both results have same values of a parameter $\kappa = 2$.
- In order to overcome the quantitative disagreement between MCT and simulation or experiment, we proposed a modification of mode coupling theory with a new parameter Δ. The origin of Δ is a neglected part in the bilinear approximation applied to the random force in the derivation of the memory function of MCT. We solved simple form of modified MCT equation and determined the value of parameter Δ so that D_S^L of modified MCT solution coincides with that of simulation result at each ϕ.
- Deviation of MCT from simulation results for $M_2(t)$ was observed in both of standard MCT and modified MCT. Origin of this problem is the convolution type projection operator method used in the derivation of MCT. In order to overcome this problem, a new type of theory based on different projection operator method and proper approximations is necessary.

論文審査結果の要旨

生体高分子の自己拡散現象は生体中の物質輸送の基礎機構であり，薬物輸送や栄養物質の吸収過程を解析する際に重要な因子である。しかし分子間の相互作用を記述するのが難しく，高濃度領域における自己拡散現象の理論的な理解はこれまで進んでいなかった。近年徳山らにより様々な生体高分子間の相互作用が簡単な相互作用でモデル化出来る可能性が見いだされ，よりマクロな系であるコロイド分散系で用いられている理論体系を用いて解析を行うことが可能となった。本研究では生体高分子分散系を単純化したモデルである改良ソフトコア系について，高濃度領域のコロイド分散系の自己拡散現象の解析に用いられるモード結合理論（ＭＣＴ）とシミュレーションの比較を行うことによりモード結合理論の問題点を明らかにし，また導出に用いられる２体近似を見直すことでモード結合理論の改良の可能性について検討を行っている。本論文は，これらの研究成果をまとめたものであり，全編６章からなる。

第１章は，序論であり，本研究の背景，目的および構成を述べている。

第２章では，本研究で用いる計算モデル，および解析手法について述べている。

第３章では，改良ソフトコアポテンシャルを基に分子間に引力が働く場合の有効相互作用を提案している。これは実際の系の相変化，およびそれを伴う系のダイナミクスを再現するために必要な拡張であり，生体高分子間の有効相互作用の開発を進める上で非常に重要な成果である。

第４章では，改良ソフトコア系のＭＣＴを導入し，その数値計算結果と計算機実験の結果の比較を行っている。特に長時間自己拡散係数の結果の比較を行い，平均場理論の解析においてこれまでの研究と同様の傾向が見られることを確かめている。また平均二乗変位の時間発展を比較することにより，ＭＣＴの解がケージ領域において計算機実験の結果からずれることを示している。このケージ領域での両者のずれは改良ソフトコア系のみならず，２成分レナードジョーンズ系でも発生することを示し，モデルの詳細に依存しない理論の本質的な欠陥である可能性を指摘している。これらは生体高分子分散系の自己拡散現象を理論的に解析する上で非常に有用な成果である。

第５章では，ＭＣＴの導出過程で用いられている２体近似を見直し，通常無視されている高次の部分に２体近似の範囲内で補正項が存在することを示している。またこれを基に改良方程式を導出し，シミュレーション結果との比較から補正を試みている。これまでの研究でも近似の見直しは図られて来たが，それらは２体以上の項を計算して精度を向上させようとする試みであった。これに対し，本研究で提案されている補正項は揺動力の時間発展演算子の置き換えに起因したものである。すなわち，これまでの研究とは異なる理論の改良の方向性を示した，学術的に極めて有益な成果である。

第６章は結論である。

以上要するに本論文は，改良ソフトコアモデル系のブラウン動力学計算において，モード結合理論の数値計算と比較を行うことによりその問題点を明らかにし，また理論の導出過程を見直すことで高次の項が二体近似に補正を与える可能性を指摘したものであり，ナノメカニクスおよび計算科学分野の発展に寄与するところが少なくない。

よって，本論文は博士（工学）の学位論文として合格と認める。